

**REMARKS**

Reconsideration of the Examiner's rejection of the present application is requested respectfully in view of the following remarks.

**STATUS OF THE CLAIMS**

Claims 1-7 were originally filed. Claims 1-5 and 7 are pending, and claim 6 was previously canceled. No claims are being amended at this time.

**SUMMARY OF OFFICE ACTION**

Claims 1-5 and 7 stand rejected under 35 U.S.C. §103(a) as being obvious over Henke et al (US 5,648,333) in view of Pavelka (EUR J Pain, 2000), McCormack (WJM 1996) and Haapala (Clin Orthop 1999).

Claims 1-5 and 7 also stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 27-28 and 30 of Henke, in view of Pavelka, McCormack and Haapala.

**THE REJECTION UNDER 35 U.S.C. §103(a)**

Claim 1 is directed to a "method for treating a degenerative joint disease...selected from the group consisting of osteoarthritis, spondylosis and cartilage atrophy". Osteoarthritis, spondylosis and cartilage atrophy are diseases which are not generally characterized as inflammatory (see, e.g., specification at page 8, lines 15 to 30). As discussed in the first paragraph on page 2 of the specification, the present invention is directed to a method for the treatment of degenerative joint diseases. The treatment is based on the discovery that such joint diseases may be promoted by the presence of matrix metalloproteinases (MMPs), such as MMP-1, -3 and -13. As a result, it has been found that matrix degradation can be inhibited significantly by the inhibition of such MMPs that have already been released or formed in the tissue. In the present invention, it has been discovered that the administration of bradykinin-antagonistic compounds in accordance with formula I

inhibits such MMPs in a patient, thus reducing matrix degradation and providing a treatment for degenerative joint diseases.

A key point of this method of treatment is that it is not merely directed at the symptoms of degenerative joint diseases, such as pain, but is specifically aimed at treating the underlying cause of these diseases, which is matrix degradation. Such a treatment is not taught or described in any of the references cited in the present Office Action, taken individually or combined.

In the present rejection, the primary reference is Henke et al, which is cited as teaching the compounds of the present invention and their use for treating arthritis and pain in a patient. Indeed, this reference is cited on page 1 and elsewhere in the present specification (under its EP number) as teaching the compounds of formula I, and their use in treating such inflammatory joint diseases as osteoarthritis or rheumatoid arthritis. As noted in the last sentence on page 1 of the specification, by reference to an article by Lerner et al, in diseases such as rheumatoid arthritis bradykinin "...does not stimulate the degradation of the cartilaginous matrix itself." With this reference in mind, it is clear that although Henke teaches that bradykinin inhibition may be useful for treating the painful symptoms of osteoarthritis or rheumatoid arthritis, there is no teaching that bradykinin inhibitors would be useful for treating bone matrix degradation, which is the underlying cause of the degenerative joint diseases to which the present invention is directed.

In the Office Action the Examiner acknowledges that Henke et al do not teach treating degenerative joint diseases such as osteoarthritis, spondyloses or cartilage atrophy. Therefore, secondary references have been cited to combine with Henke et al to provide a teaching that would render the present invention obvious. We submit that those references combined with Henke et al still do not teach the present invention.

Pavelka is cited as teaching that osteoarthritis causes pain. Applicants do not dispute that point. Indeed, Pavelka discusses various pain relievers that can be prescribed for the treatment of osteoarthritis, such as NSAIDs and opioids. The entire article is directed to methods of treating the pain of osteoarthritis. However, there is no teaching or discussion in Pavelka of treating any degenerative joint diseases such as osteoarthritis, spondyloses or cartilage atrophy.

There is no teaching or discussion in Pavelka of any method to treat bone or cartilage matrix degradation.

McCormack et al is cited as teaching that spondyloses causes pain. Applicants do not dispute this point. Yes, spondyloses causes pain, as due a myriad of diseases and conditions which afflict people. Pain is a common symptom which may be treated by pain relievers, such as the NSAIDs and opioids mentioned in Pavelka. But the more significant teaching of McCormack is in the first sentence under the heading "Pathophysiology" in column 2 of page 43, which states that "Cervical spondylosis is caused by a degeneration of the intervertebral discs, which fragment, lose water content, and collapse with normal aging." The article then proceeds to discuss a wide variety of surgical approaches to treating spondyloses. There is no teaching in the article of the administration of any medicines, much less the bradykinin inhibitors of the present invention, to treat such degeneration of intervertebral discs. There is a discussion of treating the pain associated with spondyloses by medication, but no discussion of treating the underlying matrix degeneration. Thus, it is clear that McCormack et al does not teach the method of the present invention.

Haapala et al is cited as teaching that lengthy immobilization causes cartilage atrophy, and that such atrophy causes pain. Again, Applicants do not dispute this point. However, there is no teaching or discussion in Haapala et al of any method of preventing or treating such cartilage atrophy, much less the treatment taught by the present specification of administering compounds of Formula I to inhibit MMPs, and thus treat the cartilage atrophy. Haapala et al discuss remobilization techniques, but do not present any medical treatments. Thus, this reference clearly does not teach the method of the present invention.

In discussing the above secondary references, the Examiner indicates that they show together that degenerative bone diseases cause pain. This is true. It is also true that there are many medicaments prescribed for treating pain, such as the NSAIDs and opioids discussed in Pavelka. But such pain relievers would not be expected to have any effect on the underlying bone matrix degeneration which is the cause of these diseases. Pain medications address a symptom of such diseases, not the cause.

Henke et al describe a method of treating the pain of inflammatory joint diseases such as osteoarthritis or rheumatoid arthritis. There is no teaching in Henke et al that the administration of bradykinin inhibitors would have any effect on bone or cartilage matrix degeneration. The above-cited secondary references only indicate that bone degenerative diseases are painful. These references would in no way suggest or teach that the compounds disclosed in Henke et al would be useful for treating the underlying matrix degeneration associated with these diseases. The secondary references only teach that there is pain associated with these diseases and that known pain relievers, such as NSAIDs or opioids, may be useful in relieving such pain. However, merely treating the pain associated with degenerative joint diseases is not the same as treating the underlying cause of the actual diseases themselves.

Therefore, for the reasons discussed above, it is submitted that there is no teaching in Henke et al, alone or in combination with Pavelka, McCormack et al, and/or Haapala et al, of the use of the bradykinin inhibitor compounds of Formula 1 of present claim 1 to treat degenerative bone diseases. The Examiner is respectfully requested to reconsider and withdraw the rejection of the present claims over these references.

#### THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 1-5 and 7 also stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 27-28 and 30 of Henke et al, in view of Pavelka, McCormack et al and Haapala et al. Applicants respectfully traverse this rejection.

The cited claims 27-28 and 30 of Henke et al are directed to compositions and methods for treating a variety of specified conditions including arthritis. There is nothing in these claims about the treatment of degenerative joint diseases such as osteoarthritis, spondyloses or cartilage atrophy. Although a wide variety of pathological states are included in these claims, and although degenerative joint diseases have been known for many years, yet there is no teaching or claim in Henke et al directed to the treatment of such diseases. The cited claims include a variety of inflammatory diseases, and other diseases which may cause a great deal of pain. However, there is no indication in these claims that the bradykinin inhibitors may be used for the treatment of bone or cartilage matrix degradation associated with degenerative joint diseases.

Appl. No. 10/773,772  
Amdt. Dated July 24, 2006  
Reply to Office Action of April 24, 2006

Docket No. DEAV2003/0008 US NP

As discussed above in regard to the obviousness rejection, the secondary references, Pavelka, McCormack et al and Haapala et al, only teach that degenerative joint diseases may cause pain. They do not add anything to Henke et al that would render present claims 1-5 and 7 as obvious over claims 27-28 and 30 of Henke et al. Therefore, for the reasons discussed here and in the previous part of this response, the Examiner is respectfully requested to reconsider and withdraw this obviousness-type double patenting rejection of the present claims.

For all of the above reasons, it is submitted that all of the claims in the present application are now in condition for allowance, and action to that effect is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment resulting from this Amendment to Deposit Account 18-1982.

Respectfully submitted,

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